In This Issue

Cell

Fly Pauses to Put Itself Together

PAGE 976

Paused RNA polymerase II (Pol II) is pervasive in *Drosophila* embryos and in mammalian stem cells, but its role in development is unclear. Mounia et al. show that a high level of Pol II at a gene's promoter drives its rapid and synchronous activation during *Drosophila* embryogenesis. Reduction in pausing results in the stochastic activation of *snail* expression, which disrupts invagination of the mesoderm during gastrulation.

Pluripotency by Stalemate

PAGE 963

Factors that specify differentiated cell identities (lineage specifiers) are thought be enemies of pluripotency. Shu et al. show that iPSCs can be induced from differentiated cells without pluripotency factors but simply by the forced expression of two competing factors, each specifying a different cell fate. They suggest a ''seesaw model'' in which a balance between the mutually exclusive fate-specifying forces can facilitate the cell to the pluripotent state.

Ready…Steady…Melt!

PAGE 988

Upon encounter with pathogens, lymphocytes rapidly increase expression of all genes important for immunity. How such rapid gene activation is achieved has remained unclear. By mapping single-stranded DNA throughout the genome, Kouzine et al. show that immune genes are preloaded with polymerase, but expression is restrained because the promoters are unmelted. An increase in DNA melting, partly due to changes in TFIIH levels, prompts gene expression upon activation, identifying a role for DNA melting in the regulation of eukaryotic transcription.

Histones Ac-cepted by Proteasome, No Ubiquitin Required

PAGE 1012

Proteasomes are known to catalyze the degradation of ubiquitinated proteins. During spermatogenesis, histones are degraded and replaced by protamines, yet enzymes that ubiquitinate histones have not been found. Qian et al. now show that specialized proteasomes containing the protein PA2000/Blm10 catalyze the degradation of acetylated (rather than ubiquitinated) core histones in the mammalian testes. PA2000/Blm1 proteasomes also catalyze the degradation of histones during somatic DNA repair, providing a mechanism for histone degradation that relies on acetylation rather than ubiquitination.

Regnase Reins in Autoimmunity

PAGE 1036

T cell activation must be tightly regulated to prevent autoimmunity. Uehata et al. now find that the RNase Regnase-1, previously known for its role in macrophage TLR signaling, prevents autoimmunity in mice by degrading a set of mRNAs required for T cell activation. T cell receptor (TCR) signaling promotes Regnase-1 cleavage by the Malt1 protease, stabilizing target mRNAs and enabling T cell activation, demonstrating that precise control of Regnase-1 expression is critical for the regulation of T cell activation.

Maverick PI3K Goes RHOgue

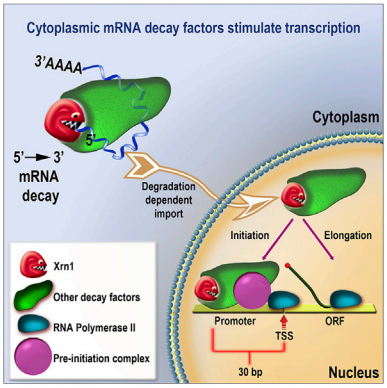
PAGE 1050

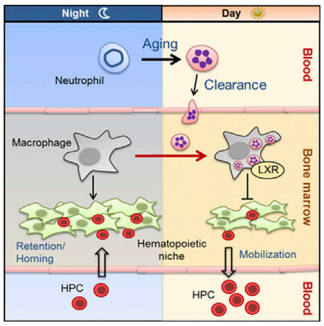
RAS proteins are important direct activators of phosphoinositide 3-kinases (PI3Ks), which play central roles in cell proliferation, migration, and metabolism. Fritsch et al. now show that the ubiquitous p110β isoform of PI3K is not regulated by RAS but is regulated instead through direct binding of the RHO family GTPases, RAC1 and CDC42. Uncoupling of p110 β from RAC results in reduced chemotaxis and resistance to experimental lung fibrosis.

Decay Factors Get Transcripts Coming and Going

PAGE 1000

Cellular mRNA levels are dictated by the balance between RNA synthesis, processing, and decay. Haimovich et al. find that, rather than relying on a flux of mRNA out of the nucleus to maintain the necessary levels of transcripts, cells utilize a feedback mechanism whereby cytoplasmic decay factors respond to mRNA levels and traffic to the nucleus to directly regulate transcription. Gene expression is thus a cyclic process in which the mRNA degradation machinery helps to regulate mRNA synthesis.





Immune System Takes the Trash Out at Night

PAGE 1025

Millions of neutrophils are removed from the circulation of healthy individuals every day, yet the physiological impact of this process is uncertain. Casanova-Acebes et al. show that neutrophils that age in the blood infiltrate the bone marrow, are taken up by macrophages, and activate LXR receptors. Elimination of neutrophils modulates the hematopoietic niche and promotes the circadian mobilization of hematopoietic precursors. These findings reveal a mechanism that couples immune and hematopoietic rhythms.

How Cancer Copes with Hunger

PAGE 1064

Nutrient deprivation is a prototypical form of cell stress. Leprivier et al. reveal that translation elongation factor 2 kinase (eEF2K) protects cells from apoptosis during acute nutrient deprivation by inhibiting the elongation step of mRNA translation. This pathway is hijacked by tumor cells to sustain growth under nutrient stress, and, in human brain tumors, elevated *eEF2K* expression is strongly correlated with poor prognosis.

How Starving Stalls Cyclin

PAGE 1080

The availability of nutrients is a key determinant of cellular growth rates. Messier et al. now identify a pathway in yeast by which nutrient status is translated, via TOR signaling, to cell-cycle progression. The activity level of an hnRNP methyltransferase is modulated by an antagonistic kinase/phosphatase pair, with nutrient-rich conditions favoring activation. This activity, in turn, leads to the accumulation of the mRNA encoding the M phase cyclin B, which is otherwise degraded.

Stepping on the cGAS to a New Class of Second Messengers

PAGE 1094

Cyclic GAMP synthase (cGAS) is a cytosolic dsDNA sensor in metazoans that synthesizes cyclic GMP-AMP (cGAMP) as a second messenger to activate the type I interferon pathway. Gao et al. combine structural and biochemical assays to demonstrate that, upon dsDNA binding, cGAS activation occurs via conformational transitions that result in the formation of a catalytically competent and accessible nucleotide-binding pocket for the generation of cGAMP. cGAMP is shown to contain A(3′,5′)pG as well as G(2′,5′)pA phosphodiester linkages and may represent a new family of metazoan 2′,5′-containing cyclic heterodinucleotide second messengers.

Malaria Parasite's Sexosomal (S'exosomal?) Signals

PAGE 1120

Cell-cell communication is a mechanism for information exchange promoting cell survival to control population density and differentiation. Regev-Rudzki et al. discover a previously unknown pathway utilized by the malaria parasite *Plasmodium falciparum* that is critical for its survival in the host and transmission to mosquitoes. They show that *P. falciparum*-infected red blood cells directly communicate within a population using exosome-like vesicles and that this communication promotes parasite differentiation to sexual forms.

Epigenomic Map for Differentiation

PAGE 1149 and PAGE 1134

Human embryonic development is controlled by both transcription factors and epigenetic mechanisms. To understand the precise role of different epigenetic mechanisms in lineage commitment, Gifford et al. and Xie et al. produce comprehensive maps of DNA methylation and histone modifications in human ES cells and seven cell types representing different lineages, revealing distinct dynamics for these marks during lineage specification. Xie et al. also report that lineage-restricted genes employ distinct epigenetic mechanisms for regulation at early and late stages of differentiation and describe a DNA methylation signature specifically marking developmental regulator genes.

View of the Starting Line for Translation

PAGE 1108

Translation initiation is a major nexus of regulatory control in eukaryotes. Hashem et al. now report the cryo-electron microscopy structure of the mammalian 43S complex associated with the DHX29 helicase that promotes mRNA scanning. The structure provides insights into eukaryote-specific aspects of translation initiation, showing how initiator tRNA, eIF2, eIF3, and DHX29 interact with the 40S subunit.